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☐	L7	l6 and $renin	3
☐	L6	L5 and (high near5 hlb)	41
☐	L5	L4 and (low near5 hlb)	70
☐	L4	L3 and l2 and l1	448
☐	L3	(hlb near3 surfactant$).ti,ab,clm.	4873
☐	L2	(hydrophilic or hydro-philic).ti,ab,clm.	122960
☐	L1	(lipophilic or lipo-philic or lipidphilic or lipid-philic).ti,ab,clm.	15940

END OF SEARCH HISTORY

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Prev Page Next

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Search Results - Record(s) 1 through 3 of 3 returned.

☐ 1. Document ID: US 20070082016 A1

L7: Entry 1 of 3 File: PGPB Apr 12, 2007

DOCUMENT-IDENTIFIER: US 20070082016 A1
TITLE: Microemulsion preconcentrate comprising a renin inhibitor

Abstract Paragraph:
The present invention relates to pharmaceutical compositions for oral administration comprising a .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitors as the active ingredient. In particular, the present invention relates to galenic formulations in the form of microemulsion preconcentrates comprising the active ingredient and at least one absorption enhancing excipient which preconcentrates provide spontaneously dispersible water-in-oil microemulsions which upon further dilution in aqueous medium, e.g., gastric fluids, convert to oil-in-water microemulsions. The present invention also relates to the processes for their preparation and to their use as medicaments.

Brief Summary Text:
[0002] The .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide derivatives are a class of potent renin inhibitors which present highly specific difficulties in relation to administration generally and galenic formulation in particular, including problems of drug bioavailability and variability in inter- and intra-subject dose response thus necessitating development of a non-conventional dosage form.

Brief Summary Text:
[0004] The use of lipid-based microemulsions to enhance the bioavailability of different drugs, including peptides, has already been described, e.g., in GB 2,222,770 and International PCT Patent Application No. WO 94/08605. Thus, GB 2,222,770 discloses microemulsions and corresponding microemulsion preconcentrates for use with the highly hydrophobic cyclosporin peptides. Accordingly, a suitable preconcentrate comprises 1,2-propylene glycol as the hydrophilic component, a caprylic-capric acid triglyceride as the lipophilic component and a mixture of a polyoxyethylene glycolated hydrogenated castor oil and glycerin monooleate (ratio 11:1) as the surfactant-cosurfactant. Such formulations may then be diluted with water, to give o/w rather than w/o microemulsions. WO 94/08605 describes self-emulsifying w/o microemulsions which comprise (i) a lipophilic phase in which the oil and the low HLB surfactant are a physical mixture of medium and long chain fatty acid components; (ii) a high HLB surfactant; and (iii) an aqueous hydrophilic phase comprising a water soluble therapeutic agent.

Brief Summary Text:
[0010] In accordance with the present invention it has now been found that stable pharmaceutical compositions with .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitors, having particularly interesting bioavailability characteristics and reduced variability in inter- and intra-subject

bioavailability parameters, are obtainable as microemulsion preconcentrates, in particular, as w/o preconcentrates. The compositions of the present invention comprise at least one excipient that enhance the oral absorption of the active ingredient either by inhibition of efflux or by enhancing transcellular absorption, e.g., by increasing membrane fluidity, and thereby would substantially reduce the difficulties encountered previously. It has been shown that the compositions in accordance with the present invention may enable effective dosaging with concomitant enhancement as well as reduced variability of absorption/bioavailability levels for and between individual subjects. Thus, the invention may achieve effective therapy with tolerable dosage levels of such .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide derivatives, and may permit closer standardization and optimization of daily dosage requirements for each individual. Consequently, occurrence of potential undesirable side-effects may be diminished and overall cost of therapy may be reduced.

Brief Summary Text:
[0011] The .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide derivatives to which the present invention applies are any of those having renin inhibitory activity and, therefore, pharmaceutical utility, e.g., as therapeutic agents for the treatment of hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders.

Brief Summary Text:
[0012] Accordingly, the present invention provides a pharmaceutical composition comprising a 8-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor as the active ingredient in an absorption enhancing carrier medium comprising:

Brief Summary Text:
(b) a high HLB surfactant; and

Brief Summary Text:
[0013] Preferably, the lipophilic component comprises a low HLB surfactant.

Brief Summary Text:
[0014] More preferably, the lipophilic component comprises a low HLB surfactant which is based on a medium or a long chain fatty acid, or a mixture of fatty acids thereof, and an oil which is a medium or a long chain fatty acid triglyceride, or a mixture of triglycerides thereof.

Brief Summary Text:
[0015] Most preferably, the lipophilic component comprises a low HLB surfactant which is based on a medium chain fatty acid, or a mixture of fatty acids thereof, and an oil which is a medium chain fatty acid triglyceride, or a mixture of triglycerides thereof.

Brief Summary Text:
[0017] Advantageously, the components of the absorption enhancing carrier medium of the present invention may all be composed of absorption enhancing excipients. However, only one absorption enhancing component may be sufficient, e.g., the high HLB surfactant.

Brief Summary Text:
[0019] Preferably, a .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide

renin inhibitor of the present invention has the formula wherein R.sub.1 is C.sub.1-4alkoxy-C.sub.1-4alkoxy or C.sub.1-4alkoxy-C.sub.1-4alkyl; R.sub.2 is C.sub.1-4alkyl or C.sub.1-4alkoxy; and R.sub.3 and R.sub.4 are independently branched C.sub.3-4alkyl; or a pharmaceutically acceptable salt thereof.

Brief Summary Text:
[0020] More preferably, the .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor of the present invention is a compound of formula (I) wherein R.sub.1 is 3-methoxypropoxy; R.sub.2 is methoxy; and R.sub.3 and R.sub.4 are isopropyl; or a pharmaceutically acceptable salt thereof.

Brief Summary Text:
[0021] Most preferably, the .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor of the present invention is (2S,4S,5S,7S)-5-amino-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxy-pro- poxy)-benzyl]-8-methyl-nonanoic acid (2-carbamoyl-2-methyl-propyl)-amide hemifumarate, also known as aliskiren.

Brief Summary Text:
[0031] Suitable low HLB surfactants for use in the present invention include, put are not limited to, fatty acid mono- and diglycerides, as well as mixtures thereof, and may also comprise a small amount by weight of free fatty acid. The mono- and diglycerides may each include blends of different fatty acid mono- and diglycerides.

Brief Summary Text:
[0032] Suitable medium chain fatty acid mono- and diglycerides are formed from caprylic and capric acids. Suitable blends comprise from about 50 to 100% caprylic acid and from about 0 to about 50% capric acid mono and/or diglycerides. Suitable commercial sources of these include, but are not limited to, absorption enhancing low HLB surfactants available under the trade name CAPMUL (Karlsham Lipid Specialties, Columbus Ohio), e.g, CAPMUL MCM which comprises monoglycerides (77.4%), diglycerides (21%) and free glycerol (1.6%), with a fatty acid composition of caproic acid (3.2%), caprylic acid (66.8%), capric acid (29.6%), lauric acid (0.3%) and palmitic acid (0.1%) and CAPMUL MCM C8 which has monoglycerides (70-90%), diglycerides (10-30%) and free glycerol (2-4%), with a fatty acid composition which comprises at least 98% of caprylic acid (manufacturers data).

Brief Summary Text:
[0035] Preferably, the low HLB surfactant will have an HLB value in the range of from about 2.5 to about 6, e.g., the HLB value of CAPMUL MCM is about 5.5.

Brief Summary Text:
[0036] Suitably, the lipophilic phase comprising the oil and the low HLB surfactant together may be present from about 15 to about 80% by weight of the total composition of the present invention, preferably, from about 20 to about 70% by weight and, more preferably, from about 30% to about 60% by weight.

Brief Summary Text:
[0037] The high HLB surfactants suitable for use in the present invention include, but are not limited to, non-ionic efflux inhibiting and thereby absorption enhancing surfactants such as: [0038] (a) Polyoxyethylene fatty acid esters, e.g., polyoxyethylene stearic acid esters of the type available under the trade name MYRJ, e.g., MYRJ 52 (a polyoxyethylene 40 stearate). Other related products include polyethoxylated saturated hydroxy fatty acids which may be produced by reacting a saturated hydroxy fatty acid, e.g., C.sub.18 to C.sub.20 fatty acid, with ethylene oxide or polyethylene glycol. Suitable examples for the present invention include those known in the art and commercially available, e.g., from the BASF company under the trade mark SOLUTOL. Especially preferred is SOLUTOL HS15 which is known, e.g., from the BASF technical leaflet MEF 151E (1986), to comprise of about 70% polyethoxylated 12-hydroxystearate by weight and about 30% by weight unesterified

polyethylene glycol component; [0039] (b) Polyoxyetheylene-sorbitan fatty acid esters (polysorbates), e.g., the mono- and trilauryl, palmityl, stearyl and oleyl esters, for instance the polyoxyethylene sorbitan monooleates available under the trade name of TWEEN, such as TWEEN 20, 21, 40, 60, 61, 65, 80, 81 and 85, of which class TWEEN 80 (polysorbat 80) is especially preferred; [0040] (c) Reaction products of a natural or hydrogenated castor oil and ethylene oxide. The natural or hydrogenated castor oil may be reacted with ethylene oxide in a molar ratio of from about 1:35 to about 1:60, with optional removal of the polyethyleneglycol component from the products. Various such surfactants are commercially available. Particularly suitable surfactants include polyethyleneglycol-hydrogenated castor oils available under the trade name CREMOPHOR, e.g., CREMOPHOR RH 40 (polyoxyl 40 hydrogenated castor oil) and CREMOPHOR EL (polyoxyl 35 castor oil); [0041] (d) Polyoxyethylene-polyoxypropylene co-polymers and block co-polymers, poloxamers, e.g., of the type known and commercially available under the trade names PLURONIC, LUTROL and MONOLAN. An especially preferred product of this class is PLURONIC F68 (poloxamer 188) from BASF, having a melting point of about 52.degree. C. and a molecular weight of about 6800 to 8975; [0042] (e) Polyoxyethylene glycol long-chain alkyl ethers, such as polyoxyethylated glycol lauryl ether; [0043] (f) Polyoxyethylene glycol long-chain alkyl esters, such as PEG-monostearate; and [0044] (g) Water soluble tocopheryl polyethylene glycol succinic acid esters (TPGS), e.g., those with a polymerization number ca 1000, e.g., VITAMIN E-TPGS, available from Eastman Fine Chemicals Kingsport, Texas, USA.

Brief Summary Text:
[0045] For use herein, the high HLB surfactant preferably has an HLB value in the range of 13 to 20.

Brief Summary Text:
[0046] The high HLB surfactant may comprise from about 5 to about 60% by weight of the total composition of the present invention, preferably, from about 10 to about 50% by weight.

Brief Summary Text:
[0047] Preferably, the blend of low and high HLB surfactants will have an HLB value in the range of from about 7 to about 15, more preferably from about 8 to about 13.

Brief Summary Text:
[0050] Preferably the relative proportions of the lipophilic component, the hydrophilic component, and the high HLB surfactant lie within the "Microemulsion" region on a standard three way plot graph. These phase diagrams may be generated in a conventional manner as described, e.g., in GB 2,222,770 and International PCT Patent Application No. WO 96/13273.

Brief Summary Text:
[0062] The microemulsion preconcentrates of the present invention, preferably, in the form of a w/o microemulsion, are formed spontaneously or substantially spontaneously when their components are brought into contact, that is without the application of substantial energy supply. For instance, in the absence of high shear energy such as imparted by homogenization and/or microfluidization or other mechanical agitation. Accordingly, the microemulsion preconcentrates may be readily prepared by the simple process of admixing appropriate quantities with gentle mixing or stirring if necessary to ensure thorough mixing. Preferably, the therapeutic agent is dissolved in the hydrophilic phase, either directly or by dilution of a stock solution thereof, and this may then be added to a pre-mixed combination of the oil and the low HLB surfactant with mixing, followed by the high HLB surfactant or vice versa. Alternatively, a drug-free microemulsion preconcentrate may be initially prepared by admixing the oil, the low HLB surfactant, the high HLB surfactant and the hydrophilic component, to which composition may then be added the therapeutic agent. Whilst higher temperatures

(40-60.degree. C.) may be needed to solubilize all components during the preparation of the microemulsion preconcentrate, the preferred systems may be formulated at room temperature.

Brief Summary Text:
[0063] As defined herein, the active ingredient or the therapeutic agent refers to any .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide derivative which exhibits renin inhibitory activity as may be determined by standard in vitro and in vivo tests known in the art, e.g., by those disclosed in U.S. Pat. No. 5,559,111. The .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide derivatives may be prepared according to literature procedures, e.g., those described in U.S. Pat. No. 5,559,111.

Brief Summary Text:
[0064] In a preferred aspect, the present invention provides pharmaceutical compositions in the form of microemulsion preconcentrates comprising at least one absorption enhancing excipient which compositions provide spontaneously dispersible w/o microemulsions which upon further dilution in aqueous medium, e.g., gastric fluids, convert to o/w microemulsions, and a .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor which may be orally administered and which will retain its biological activity, thereby overcoming the disadvantages of earlier formulations in which the bioavailability of the .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide derivatives has been less than satisfactory.

Brief Summary Text:
[0068] Ultimately, the present invention provides for the use of a fatty acid triglyceride, a low HLB surfactant, a high HLB surfactant, a hydrophilic component and a therapeutic agent as hereinbefore defined in the manufacture of a medicament.

Brief Summary Text:
[0069] Thus, the present invention relates to use of pharmaceutical compositions as described herein above for the manufacture of a medicament for the treatment of conditions mediated by renin activity, preferably, hypertension, atherosclerosis, unstable coronary syndrome, congestive heart failure, cardiac hypertrophy, cardiac fibrosis, cardiomyopathy postinfarction, unstable coronary syndrome, diastolic dysfunction, chronic kidney disease, hepatic fibrosis, complications resulting from diabetes, such as nephropathy, vasculopathy and neuropathy, diseases of the coronary vessels, restenosis following angioplasty, raised intra-ocular pressure, glaucoma, abnormal vascular growth, hyperaldosteronism, cognitive impairment, alzheimers, dementia, anxiety states and cognitive disorders.

Brief Summary Text:
[0072] The microemulsion preconcentrates of the illustrative Examples may generally be prepared by first dissolving the appropriate amount of the therapeutic agent, e.g., aliskiren, in the hydrophilic component, e.g., PEG 300, with stirring if necessary to obtain complete dissolution. The hydrophilic phase containing the drug is then added to the appropriate amounts (by weight) of a mixture of the oil and the low HLB surfactant, to which is then added the high HLB surfactant, with gentle stirring. Alternatively, the hydrophilic phase containing the drug is added to the high HLB surfactant and following upon complete mixing, this is added to the oil plus low HLB surfactant mixture. If necessary, the drug-containing microemulsion preconcentrate is then diluted with the corresponding drug-free microemulsion to adjust the concentration of the drug.

CLAIMS:

1. A pharmaceutical composition for oral administration comprising a .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor in an absorption

enhancing carrier medium comprising: (a) a lipophilic component; (b) a high HLB surfactant; and (c) a hydrophilic component; which composition upon admixing forms a stable microemulsion preconcentrate.

2. A pharmaceutical composition according to claim 1, wherein the lipophilic component comprises a low HLB surfactant.

3. A pharmaceutical composition according to claim 2, wherein the lipophilic component comprises a low HLB surfactant which is a based on a medium or a long chain fatty acid, or a mixture of fatty acids thereof, and an oil which is a medium or a long chain fatty acid triglyceride, or a mixture of triglycerides thereof.

4. A pharmaceutical composition according to claim 3, wherein the lipophilic component comprises a low HLB surfactant which is based on a medium chain fatty acid, or a mixture of fatty acids thereof, and an oil which is a medium chain fatty acid triglyceride, or a mixture of triglycerides thereof.

6. A pharmaceutical composition according to claim 4, wherein the .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor has the formula wherein R.sub.1 is C.sub.1-4alkoxy-C.sub.1-4alkoxy or C.sub.1-4alkoxy-C.sub.1-4alkyl; R.sub.2 is C.sub.1-4alkyl or C.sub.1-4alkoxy; and R.sub.3 and R.sub.4 are independently branched C.sub.3-4alkyl; or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition according to claim 6, wherein the .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor is a compound of formula (I) wherein R.sub.1 is 3-methoxypropoxy; R.sub.2 is methoxy; and R.sub.3 and R.sub.4 are isopropyl; or a pharmaceutically acceptable salt thereof.

8. A pharmaceutical composition according to claim 7, wherein the .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor is (2S,4S,5S,7S)-5-amino-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxy-pro- poxy)-benzyl]-8-methyl-nonanoic acid (2-carbamoyl-2-methyl-propyl)-amide hemifumarate.

10. A pharmaceutical composition according to claim 6, wherein the medium chain fatty acids of the lipophilic component have from 8 to 12 carbon atoms.

12. A pharmaceutical composition according to claim 6, wherein the low HLB surfactant has an HLB value ranging from about 2.5 to about 6.

13. A pharmaceutical composition according to claim 6, wherein the high HLB surfactant has an HLB value ranging from about 13 to about 20.

14. A pharmaceutical composition according to claim 13, wherein the high HLB surfactant is selected from polysorbat 80, macrogol-15 hydroxystearate, vitamin E-TPGS and polyoxyl 40 hydrogenated castor oil.

15. A pharmaceutical composition according to claim 6, wherein the hydrophilic phase comprises PEG 300.

16. A pharmaceutical composition according to claim 15, wherein the medium chain fatty acids of the lipophilic component have from 8 to 12 carbon atoms.

17. A pharmaceutical composition according to claim 16, wherein the low HLB surfactant has an HLB value ranging from about 2.5 to about 6.

18. A pharmaceutical composition according to claim 17, wherein the high HLB surfactant has an HLB value ranging from about 13 to about 20.

19. A pharmaceutical composition according to claim 18, wherein the .delta.-amino-

.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor is a compound of formula (I) wherein R.sub.1 is 3-methoxypropoxy; R.sub.2 is methoxy; and R.sub.3 and R.sub.4 are isopropyl; or a pharmaceutically acceptable salt thereof.

21. A pharmaceutical composition according to claim 19, wherein the high HLB surfactant is selected from polysorbat 80, macrogol-15 hydroxystearate, vitamin E-TPGS and polyoxyl 40 hydrogenated castor oil.

22. A pharmaceutical composition according to claim 19, wherein the .delta.-amino-.gamma.-hydroxy-.omega.-aryl-alkanoic acid amide renin inhibitor is (2S,4S,5S,7S)-5-amino-4-hydroxy-2-isopropyl-7-[4-methoxy-3-(3-methoxy-pro- poxy)-benzyl]-8-methyl-nonanoic acid (2-carbamoyl-2-methyl-propyl)-amide hemifumarate.

24. A pharmaceutical composition according to claim 23, wherein the high HLB surfactant is selected from polysorbat 80, macrogol-15 hydroxystearate, vitamin E-TPGS and polyoxyl 40 hydrogenated castor oil.

Full | Title | Citation | Front | Review | Classification | Date | Reference | Sequences | Attachments | Claims | KWIC | Draw D

☐ 2. Document ID: WO 9408605 A1, EP 666752 A4, EP 666752 A1, JP 08502492 W

L7: Entry 2 of 3 File: DWPI Apr 28, 1994

DERWENT-ACC-NO: 1994-150935
DERWENT-WEEK: 199702

TITLE: Water-in-oil microemulsion as oral or topical drug delivery vehicle - used for peptide(s), insulin, calcitonin, somatostatin, growth hormone, etc, and enhances oral bio:availability

INVENTOR: CONSTANTINIDES, P; CONSTANTINIDES, P P

PRIORITY-DATA: 1992US-0962957 (October 16, 1992)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9408605 A1	April 28, 1994	E	038	A61K037/00
EP 666752 A4	September 11, 1996		000	A61K037/00
EP 666752 A1	August 16, 1995	E	000	A61K037/00
JP 08502492 W	March 19, 1996		043	A61K009/107

INT-CL (IPC): A61K 9/107; A61K 37/00; A61K 38/00; A61K 38/04; A61K 38/23; A61K 38/28; A61K 47/14

Full | Title | Citation | Front | Review | Classification | Date | Reference | Claims | KWIC | Draw D

☐ 3. Document ID: WO 9408603 A1, EP 671929 A4, EP 671929 A1, JP 08502490 W

L7: Entry 3 of 3 File: DWPI Apr 28, 1994

DERWENT-ACC-NO: 1994-150933
DERWENT-WEEK: 199707

TITLE: Water in oil microemulsion useful as oral or topical drug delivery vehicle partic. for peptide(s) - comprises lipophilic phase contg inter-esterified tri:glyceride and low HLB surfactant, high HLB surfactant, aq hydrophilic phase etc

INVENTOR: CONSTANTINIDES, P; CONSTANTINIDES, P P

PRIORITY-DATA: 1992US-0962956 (October 16, 1992)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9408603 A1	April 28, 1994	E	034	A61K037/00
EP 671929 A4	September 25, 1996		000	A61K037/00
EP 671929 A1	September 20, 1995	E	000	A61K037/00
JP 08502490 W	March 19, 1996		039	A61K047/06

INT-CL (IPC): A61K 37/00; A61K 37/02; A61K 37/26; A61K 38/00; A61K 38/04; A61K 38/11; A61K 38/23; A61K 38/28; A61K 47/06

Term	Documents
$RENIN	0
RENIN	9812
ARENIN	7
CARENIN	3
ALPHA-CARENIN	2
BETA-CARENIN	1
SCIHARENIN	1
I5FIARENIN	1
KARENIN	7
CIS-KARENIN	2
(L6 AND $RENIN).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	3

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Display Format: - Change Format

1. Document ID: IN 200602180 P4, WO 2005058291 A1, AU 2004298758 A1, EP 1729748 A1, MX 2006006926 A1, BR 200417535 A, US 20070082016 A1, JP 2007514697 W, CN 1893932 A, KR 2006130072 A

L8: Entry 1 of 1 File: DWPI Jun 8, 2007

DERWENT-ACC-NO: 2005-479200
DERWENT-WEEK: 200748

TITLE: Oral composition useful to treat conditions associated with renin activity (e.g. hypertension), comprising delta-amino-gamma-hydroxy-omega-aryl-alka- noic acid amide renin inhibitor in absorption enhancing medium

INVENTOR: OTTINGER, I

PRIORITY-DATA: 2004US-547676P (February 25, 2004), 2003US-531562P (December 19, 2003), 2006US-0580258 (May 24, 2006)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
IN 200602180 P4	June 8, 2007	E	000	A61K031/00
WO 2005058291 A1	June 30, 2005	E	027	A61K031/00
AU 2004298758 A1	June 30, 2005		000	A61K009/107
EP 1729748 A1	December 13, 2006	E	000	A61K031/00
MX 2006006926 A1	September 1, 2006		000	A61K031/00
BR 200417535 A	March 27, 2007		000	A61K031/00
US 20070082016 A1	April 12, 2007		000	A61K031/165
JP 2007514697 W	June 7, 2007		022	A61K009/107
CN 1893932 A	January 10, 2007		000	A61K031/00
KR 2006130072 A	December 18, 2006		000	A61K009/107

INT-CL (IPC): A61K 9/00; A61K 9/107; A61K 31/00; A61K 31/16; A61K 31/165; A61K 47/12; A61K 47/14; A61K 47/22; A61K 47/34; A61P 3/00; A61P 3/10; A61P 5/00; A61P 5/42; A61P 9/00; A61P 9/04; A61P 9/10; A61P 9/12; A61P 13/00; A61P 13/12; A61P 25/00; A61P 25/22; A61P 25/28; A61P 27/00; A61P 27/06; A61P 43/00

Term	Documents
$RENIN	0
RENIN	9812
ARENIN	7
CARENIN	3
ALPHA-CARENIN	2
BETA-CARENIN	1
SCIHARENIN	1

I5FIARENIN	1
KARENIN	7
CIS-KARENIN	2
(L4 AND $RENIN NOT L7).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	1

There are more results than shown above. Click here to view the entire set.

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